LETTERS TO THE EDITOR

BCG vaccination by multipuncture method

I write in response to the article by Al Jarad et al on this topic. The first study to compare the efficacy of BCG vaccination and its side effects using the Bignal multipuncture device with the reusable handle and disposable heads was the pilot study of neonatal BCG vaccination carried out in 1992 for the Department of Health in our health authority.1

In previous studies in neonates and children under two, referenced in the paper by Al Jarad et al, an 18–20 needle percutaneous head gave approximately the same degree of tuberculin conversion as did intradermal vaccination but, to achieve this in older children and adults, 36–40 punctures were required. This would require either a 40 needle head or a double vaccination with two × 18–20 needles. This is why percutaneous BCG is currently only licensed for children aged under two years. Although in neonates2 and in Al Jarad’s study3 in older children the rate of tuberculin conversion was lower with percutaneous than with intradermal vaccination, tuberculin conversion does not necessarily equate to lower efficacy. In the early studies on BCG the protective efficacy of the vaccine was related to the presence of a scar after vaccination, but not to the tuberculin test result after vaccination. Those with a BCG scar but a negative post vaccination tuberculin test—that is, no tuberculin conversion—had the same degree of protection against tuberculosis over the 15 years following vaccination as did those with a scar and a positive post vaccination tuberculin test.1

The multipuncture method is undoubtedly easier to use in neonates because their very thin skin makes intradermal vaccination difficult, and also in nervous teenagers. Further, long term studies on large numbers of subjects would be required to determine whether the technique using only 18 needles in older children is as effective as intradermal vaccination. Such studies may well prove to be unnecessary. The PHLS system for enhanced tuberculin surveillance begun after neonatal percutaneous BCG vaccination of selective at risk groups, however, would still be required.

L PETER ORMEROD Chest Clinic, Blackburn Royal Infirmary, Blackburn, Lancashire B21 3LR, UK


AUTHORS’ REPLY To our knowledge our study4 was the first to compare the Bignal device with the conventional device in the multipuncture technique in schoolchildren. We were interested in assessing its efficacy in this particular group as we felt that the multipuncture technique would allow us to protect more schoolchildren in a part of London where it is difficult to access this population. The studies by Cundall et al and later by Ormerod and Palmer4 made the same comparison in neonates and small children.

We agree (and stated) that the 18 needle device may not be sufficient to convey a similar conversion rate of the tuberculin test. The manufacturers were unable to produce 40 needle heads as they would require an unacceptably high pressure on the handle to release the needles. We feel that applying two successive punctures with an 18 needle head on the same skin area would not be practicable as the head comes off and would need to be changed after each application. In addition, schoolchildren (and the operators) would not appreciate two applications.

Dr Ormerod’s statement on the BCG scar being a predictor of protection may be appropriate for the intradermal method. In our study the BCG scar in children who received the multipuncture method was not visible in under one fifth of children.

Dr Ormerod is in agreement with our statement that the conversion of the tuberculin test does not equate to protection from tuberculosis, but it is frequently used as an indirect measure of the efficacy of BCG vaccination.

We strongly support the PHLS system for enhanced tuberculin surveillance in the UK, but unfortunately we do not hold out Dr Ormerod’s optimism that it will indicate that unselective BCG vaccination can be discontinued in boroughs and countries where notification rates of tuberculosis are high. Further studies on the protective values of multipuncture BCG may still be appropriate.

Correspondence to: Dr N Al Jarad

NABIL AL JARAD
Department of Respiratory Medicine, Bristol Royal Infirmary, Bristol BS2 8HT, UK

D W EMPEY
Royal London Hospital Trust, London E1 1BB, UK

G DUCKWORTH
Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, UK


LETTERS TO THE EDITOR

Respiratory care units for non-invasive mechanical ventilation in motor neurone disease

We read with interest the review by Polkey et al pointing out the need to use all means possible to enable patients with motor neurone disease to achieve the best quality of life.

The authors state that, in order to maintain 24 hour ventilatory support, nasal ventilation must be complemented with alternative strategies during the day that are not suitable for widespread use in district general hospitals. We consider that it is possible to maintain 24 hour non-invasive ventilation in patients with motor neurone disease if nasal ventilation is combined with other non-invasive techniques such as mouth piece ventilation or a pneumobelt, and with manual or mechanical expiratory muscle aids to clear secretions in those patients whose weakness makes spontaneous coughing ineffective.1 It is important to provide patients with motor neurone disease with mechanical ventilation because they can delay tracheostomy and additional problems in most patients with motor neurone disease and are the only way for those patients who reject tracheostomy but want ventilatory support. However, we are in agreement with Polkey et al that this treatment must be performed by trained staff in respiratory care units. Moreover, these units are the best place to prevent respiratory morbidity and mortality, to enhance cooperation between patients, relatives and caregivers, and to manage clinical and psychological problems during the terminal phase of the disease.

In our experience the care of patients with motor neurone disease outside respiratory care units needs to be improved. These patients must not be negatively discriminated against compared with other chronic patients receiving even more expensive but socially accepted treatment. We must therefore try to ensure that all patients with motor neurone disease have access to management in a respiratory care unit in order to receive standardised quality care both at hospital and at home.

EMILIO SERVERA
DIEGO PÉREZ
ELIA GÓMEZ-GERMÁN
JULIO MARÍN
Department of Pulmonary Medicine, Hospital Clínico Universitario, Universidad de Valencia, Valencia, Spain


AUTHOR’S REPLY We thank Dr Servera and colleagues for their interest in our paper. We agree that patients with motor neurone disease should have access to specialist expertise where this is necessary. However, we are also conscious that travel can be difficult for some patients with advanced disease and our experience is that, in many cases, satisfactory palliation can be achieved using non-invasive positive pressure ventilation alone. This treatment could theoretically be
provided by an interested chest physician working in a district general hospital. We recognise that, in practice, it may be difficult to identify the necessary resources and that, conversely, an under-resourced service may lead to suboptimal care; however, this is true both of district hospitals and specialist centres.

M POLKEY
Lane-Fox Unit, St Thomas’ Hospital, London SE1 7EH, UK

Asthma deaths in Scotland and in Wales

It is surprising to say the least that, although the two inquiries into asthma deaths published recently in Thorax

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made the point that most asthma deaths occurred outside hospital, and hence were not recorded in the “relative rarity” of deaths in hospital), neither addressed the question as to whether more prompt admission to a hospital with respiratory intensive care facilities could have prevented some, or even many, of the domestic deaths.

The Respiratory Unit at the Northern General Hospital in Edinburgh first addressed that question as long ago as 1968 when it inaugurated a self-admission scheme for patients known by the unit to be subject to asthmatic attacks, whereby the often long delays inherent in conventional admission procedures were bypassed with the willing cooperation of their general practitioners. The scheme was more fully described in 1975 and reports on 10 year and 15 year reviews of its progress were published in 1979

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and 1987.

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These showed that the death rate in patients admitted under the scheme was only 0.3%, substantially lower than that recorded in asthmatic patients admitted to other Edinburgh hospitals which relied on conventional admission procedures.

The asthma self-admission scheme was widely welcomed as a measure which could save lives and was copied in many other hospitals throughout the world. It received widespread administration of oxygen and fast track admission and, with the more widespread availability of domiciliary early intervention, has become an almost accepted standard in asthma deaths. The many deaths which would have been prevented by fast track admission and, with the more widespread availability of oxygen and domiciliary early intervention, have saved lives and have allowed wider use of the full range of medical and paramedical ambulance services. There are other reasons for emphasising the value of such services, as well as convincing patients and their families to manage to the occurrence of such episodes.

C E BUCKNALL
S C WRIGHT
Department of Respiratory Medicine, Gartnavel General Hospital, Glasgow G12 0YN, UK

AUTHORS’ REPLY We are aware of the work to which Dr Grant refers, and agree that self-admission schemes can prevent asthma deaths by avoiding the delays that sometimes occur with conventional admission procedures. Different versions of self-admission schemes operate throughout Wales, but there is no uniform practice and it is possible that a few deaths in our series might have been prevented if such a scheme had operated everywhere. However, in most cases it is unlikely that the outcome would have been different, particularly when patients failed to take their illness seriously, were not under the care of a respiratory physician, or had no prior history of severe attacks.

M L BURR
B H DAVIES
A JONES
J WILLIAMSON
Centres for Applied Public Health Research, University of Wales College of Medicine, Temple of Peace and Health, Cardiff CF1 3NW, UK

Nebulised fluticasone

The place of nebulised inhaled corticosteroids in the treatment of patients with asthma is difficult to assess, but Dr J M Hill’s editorial in Thorax

4

was inaccurate and below accepted standards for a major medical journal.

G R G TODD
Astrum Area Hospital, BT41 2RL, UK

Nebulised fluticasone is frequently referred to, yet all the studies referenced

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have only been published as abstracts (sponsored by the manufacturers of fluticasone) in supplements to journals. There are insufficient details for these papers to be properly scrutinised. They have not been subject to proper peer review and should have no place as the sole references for a new treatment for asthma in the editorial of a major medical journal.

Dr Hill states that “it is from a number of studies that fluticasone is twice as potent as budesonide at a mg for mg dose” but references this with a study which compares fluticasone with beclomethasone and not budesonide.

This is clearly incorrect. She forgets that different inhaling devices influence potency ratios. Thus, fluticasone in a Diskhaler may be equipotent with budesonide in a Turbodisk and, with the more widespread availability of domiciliary early intervention, has become an almost accepted standard for a major medical journal.

In the study cited, fluticasone was equipotent with budesonide at comparable doses. However, this is not true for the Diskhaler, where it is more potent than budesonide at the same dose.

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3 Grant IWB. Deaths from asthma. BMJ 1986;1:575.


7 Dose of CFC-free inhaled beclomethasone (Qvar), CSMACMA Core Protocols Pharmaco- therapy 1999:25–5.


AUTHOR’S REPLY The author thanks Dr Todd for his constructive comments on her review article.

There are few published randomised controlled trials of nebulised fluticasone or budesonide in the treatment of asthma. Despite this, these agents are being actively marketed by the pharmaceutical industry so it is vital that the debate about the place of these agents in the treatment of asthma should be held. Finally, neither the author nor the editor thinks that it is justifiable to review what evidence is available, accepting its limitations in abstract form.

The author apologises for incorrectly quoting a paper comparing the potency of budesonide and fluticasone. The correct reference is cited below. However, the author had presumed that the readers of *Thorax* would be well aware that data comparing different inhaled corticosteroids apply only to the type of inhaler used in any comparison, and that this basic principle did not require explanation.

Dr Todd’s comments about different nebuliser systems and drug solubility are well taken. However, this was a short review of the available clinical evidence for the use of nebulised corticosteroids in the treatment of patients with asthma. It was not possible to, nor did I, review nebuliser pharmacokinetics and, as Dr Todd states, there are no comparative studies of the potency ratio of nebulised corticosteroids in the treatment of asthma. Despite this, these agents are being actively marketed by the pharmaceutical industry so it is vital that the debate about the place of these agents in the treatment of asthma should be held. Finally, neither the author nor the editor thinks that it is justifiable to review what evidence is available, accepting its limitations in abstract form.

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Therapeutic equivalence of inhaled salbutamol

The meta-analysis by Hughes et al was hindered by difficulties in comparing trials that were often flawed and of varied design. The authors correctly pointed out that, in most of the studies, the use of equivalence as the null hypothesis was invalid. In addition, all but two of the studies looked at the bronchodilator effects in the presence of basal airway tone, when the top of the dose response curve for bronchodilator response occurs in mild to moderate asthma at a salbutamol dose of approximately 200 μg for chlorofluorocarbon (CFC) or hydrofluor- alkane (HFA) pressurised metered dose inhalers (pMDIs). To construct a proper dose response curve to estimate relative bronchodilator potency would therefore necessitate the use of doses much lower than 200 μg or evaluation of patients with more severe asthma. Two of the cited studies evaluated functional antagonism against histamine induced bronchoconstriction in patients with mild to moderate asthma. However, in such patients the dose response curve for broncho- protection is relatively shallow. For example, in a recent study of 72 patients with mild to moderate asthma a fourfold increment in the dose of foromterol Turbuhaler (from 6 μg to 24 μg) only resulted in a shift of methacholine hyperresponsiveness of one doubling dose.

One simple way of evaluating bioequivalent doses of inhaled salbutamol is to evaluate the relative respirable lung dose, which can be quantified as lung deposition divided by early lung absorption profile in the first 20 minutes after inhalation, expressed as the maximal plasma concentration (Cmax) for the same nominal dose.

We have therefore reviewed eight studies performed in our laboratory using an identical design in which a nominal dose of 1200 μg salbutamol was administered via different devices in healthy volunteers. Where the same device was evaluated in two or more attempt.
studies, the highest value for $C_{\text{max}}$ was used. A significant difference between devices was assumed where respective 95% confidence intervals did not overlap. The results are shown in Fig. 1.

There were no differences in lung dose between CFC-pMDI, HFA-pMDI, and the dry powder inhalers, although the Accuhaler produced lower levels than the Diskhaler. As expected, the addition of a Volumatic spacer increased the lung delivery for both CFC-pMDIs and HFA-pMDIs. When used in combination with a Volumatic spacer there was greater delivery with HFA than with CFC. The Sidestream nebuliser resulted in a lower relative lung dose than any of the other devices. However, if an adjustment is made to reflect the usual 2500 µg nominal dose administered by nebuliser ($C_{\text{max}} = 2.52$ ng/ml), the lung dose is similar to the adjusted value for a 400 µg nominal dose from a Nebuhaler spacer with HFA-pMDI ($C_{\text{max}} = 2.96$ ng/ml).

Although decreased airway calibre in asthmatic patients will reduce the lung dose of salbutamol from a given device, the relative difference in lung bioavailability between devices will remain the same and is related to the bronchodilator response. Measurement of the lung bioavailability of salbutamol in healthy subjects may therefore represent a simple in vivo method for preliminary quantification of the relative lung dose from different inhaler devices to select rational doses for subsequent clinical equivalence studies in asthmatic patients.

STEPHEN J FOWLER
BRIAN J LIPWORTH
Asthma and Allergy Research Group,
Department of Clinical Pharmacology and Therapeutics,
Ninewells Hospital and Medical School,
Dundee DD1 9SY, UK
email: b.j.lipworth@dundee.ac.uk

NOTICE

International Pediatric Respiratory and Allergy Congress

The International Pediatric Respiratory and Allergy Congress will be held on 1–4 April 2001 at the Prague Congress Center, Prague, Czech Republic. For further information contact the Congress Secretariat at the Congress Centre, Czech Medical Society, JEP Sokolská 31, CZ-120 26 Prague, Czech Republic. Telephone +4202 296889 or +4202 297271; fax +4202 294610 or +4202 2416836. Email: lonekova@cls.cz